Docket No.: AGALIN 3.0-003 II
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Fishman et al.

Application No.: 10/631,911 Confirmation No.: 9615

Filed: July 31, 2003 Art Unit: 3743

For: METHODS FOR EASING PAIN AND ANXIETY FROM ATRIAL OR VENTRICULAR DEFIBRILLATION

Examiner: T. K. Mitchell

DECLARATION OF ROYCE S. FISHMAN

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. The undersigned Royce S. Fishman avers that he is one of the co-inventors listed in the above-identified pending U.S. Patent Application No. 10/631,911, which was filed on August 31, 2003, and which claims priority from earlier Provisional Application No. 60/404,830, which was filed on August 20, 2002.

2. I am familiar with the prosecution of Application No. 10/631,911 in the U.S. Patent and Trademark Office, and in particular the fact that the Official Actions therein, including the latest official action dated June 12, 2006, include rejections in which Ujhelyi *et al.*, U.S. Patent No. 6,728,574 ("the '574 Patent"), was cited as a reference against the pending claims in this application.

3. Significant portions of the disclosure of the '574 Patent, and particularly those which appear to be referred to by the Examiner, were learned by the inventors of the '574 Patent, including Mr. Ujhelyi, from the inventors of this

present application; namely, Messrs. Fishman and Ujhelyi. These include, for example, specific reference therein to the inhalation of nitrous oxide and the specific nature of a device for the delivery of nitrous oxide by means of self-administration by an outpatient. Thus, prior to October 19, 2001, the filing date of the '574 Patent, Messrs. Fishman and Ujhelyi had already invented the present invention, and portions of this invention were disclosed to the applicants of the '574 Patent, which became part of that disclosure. Thus, where the '574 Patent specifically refers to a particular type of inhalation therapy, particularly utilizing nitrous oxide, such as at column 3, lines 60-67, and column 4, lines 1-8 and lines 28-58, this disclosure constitutes disclosure of the applicants' invention.

4. Prior to the filing date of the '574 Patent, namely October 19, 2001, I and my co-inventor, Mr. Ujhelyi, had fully conceived of the invention which is the subject of pending U.S. Patent Application No. 10/631,911, including a method of easing a patient's pain and anxiety from atrial or ventricular defibrillation by causing the patient to inhale an effective amount of a medical gas such as N_2O/O_2 or N_2O/O_2/He or $N_2O/O_2/N_2$, for a short period of time, such as less than six minutes, activating a defibrillation device in connection with the patient being under the influence of the medical gas, and remotely communicating information relating to actuation of the defibrillation device, whereby a remotely located third party can assist the patient in inhaling the medical gas or in activating the defibrillation device, and wherein the inhalation of the medical gas produces in the patient analgesia, anxiolysis and/or anterograde amnesia immediately prior to, during and immediately after activating the defibrillation device.

5. Annexed hereto as Exhibit A is a true copy of a presentation which was prepared prior to October 19, 2000, for

presentation by me to Medronic, Inc., the assignee of the '574 Patent, and which was in fact actually presented to Medtronic, Inc. prior to October 19, 2001, with the actual dates of same blacked out therefrom.

6. From a date prior to October 19, 2001, until the filing of Provisional Application No. 60/404,830 on August 20, 2002, my co-inventor and I diligently pursued the constructive reduction to practice of our invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 12/7/06

ROYCE S. FISHMAN

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NITROUS OXIDE

THE IDEAL
ANALGESIC AND ANXIOLTYIC

AGA LINDE BUSINESS CONFIDENTIAL

FOR MEDTRONIC

FOR INTERNAL REFERENCE AND USE ONLY

R. FISHMAN
CORPORATE DIRECTOR
PRODUCT DEVELOPMENT AND STRATEGIC MARKETING
AGA LINDE HEALTHCARE

WHO IS AGA LINDE HEALTHCARE (ALH)

ALH is a $320 million+ dollar global healthcare business.

It produces and sells gases used in hospital and outpatient based clinical medicine and operates homecare respiratory therapy services.

Within the medical gas industry, only ALH is focused on the active identification and development of new pharmaceutical and medical device applications for gases.

ALH was the first company to file and obtain an NDA on a gas based pharmaceutical, Nitric Oxide.

ALH is the world leader through INO Therapeutics, a division of ALH, in the medical use of Nitric Oxide.

ALH management includes physicians, medical patent holders and pharmaceutical marketers with major vendor experience.

N20 HAS A LONG HISTORY OF HUMAN USE AS AN ANALGESIC

1772 Discovery by J. Priestly

1798 First inhaled by H. Davy for relief of infected tooth

1844 First used by Wells in practical dentistry with air ← First Clinical Use As An Analgesic

1868 First reported used in dentistry with oxygen

1881 Klikowitsch reports on first use in labor

1887 First marketed device to blend N20 and O2 and to deliver mixture

1897 Colton reports on 193,000 dental cases using N20 for analgesia with no problems

1966 First published report on use of N20 analgesia for a non-dental procedure (podiatry)

1969 Baskett reports on first use of factory prepared premix in single cylinder of 50% N20/50%02 in UK

1970 First use of factory prepared premix in ambulance service UK

1970 First device for blending N20 and O2 with O2 fail safe mechanism

1972 Ruben, a Danish researcher, cites 3 million dental cases using N20 for analgesia

1976 Thompson and Lown first report on use of N20/O2 mixture in U.S., for myocardial infarct pain

WHAT IS UNIQUE ABOUT NITROUS OXIDE AS AN ANALGESIC PHARMACEUTICAL

The lungs are the route of administration and elimination

Dose is a function of concentration, duration of administration and rate of elimination

The rate of elimination can and must be controlled

The dose must be delivered in a closed circuit (facemask <--> patient) where equilibrium is reached between the delivered dose and the dose in the bloodstream

N20 rapidly enters the bloodstream via the lungs and rapidly takes effect

When the closed circuit is ended, N20 rapidly leaves the bloodstream via the lungs and the effect rapidly dissipates

STAGES OF ANESTHESIA

Stage 1
Analgesia/conscious sedation

Stage 2
Excitement/delirium

Stage 3
Planes of surgical anesthesia

Stage 4
Medullary paralysis/death

STAGES OF N20 ANALGESIA

Linde

Zone 1 6-25%: moderate with few side effects

Zone 2 26-45%: more potent analgesia and psychological side effects (anxiolytic)

Zone 3 46-65%: almost total analgesia and amnesia but contact with patient is maintained; person does not become unresponsive until 60-65%

Standard analgesic/anxiolytic mixture for EMS and birthing use is 50% N20/50% O2 self administered by patient with demand valve vs. continuous flow

Zone 4 66-85%: light anesthesia, contact with the patient is no longer possible

Approx. ranges and effects; based on masked anesthesia study under controlled hospital operating room conditions

N20 COMPARED TO MORPHINE

The literature reports that:

- 20% N20 is equivalent in pain relief to 15mg morphine IM in normal volunteers
- 25% N20 is equivalent in pain relief to 10mg morphine in patients with moderate post operative pain
- 50% N20 is equivalent in pain relief to 10mg of morphine in typical moderate to severe EMS or birthing pain (where high levels of anxiety also exist)

50% N20 HAS A LONG HISTORY OF ACUTE ANALGESIC AND ANXIOLYTIC USE FOR NON-DENTAL PROCEDURES

A factory prepared and QC'd pharmaceutical mixture of 50% N20/50% O2 in a single compressed gas cylinder, self administered by the patient using a demand valve

- Has been part of "the standard of care" for over 20 years in the UK, Australia, New Zealand and large parts of Canada for birthing and in ambulance services (EMS)

This same product also has a "long recent" history of use in volume within other large areas of Europe, and S. America

There is renewed interest, particularly in Europe, about its use in minor surgical procedures

AGA LINDE HEALTHCARE HAS EXTENSIVE EXPERIENCE WITH A PHARMA FACTORY PREPARED MIXTURE OF 50% N20/50% O2 AS AN ANALGESIC AND ANXIOLYTIC IN EUROPE AND S. AMERICA

A study on the use of our product in France has been submitted to the NEW ENGLAND JOURNAL OF MEDICINE *

- Covering over 5000 inhalation administrations to pediatric patients
- 30% were during emergency room based procedures
- 70% routine minor/surgical procedures
- Most inhalation durations were less than 19 minutes

* Currently in advanced stages of review

CURRENT ACUTE TERM USE OF 50% N20 AS AN ANALGESIC/ANXIOLYTIC

- Angina/chest pains
- Applying plaster casts
- Back spasms
- Birthing
- Burn debridement
- Cancer (terminal) palliative pain management at home
- Extraction from damaged vehicles/collapsed buildings
- Incision and draining of abscess
- Insertion of chest drainage tubes
- Joint injections in pediatric rheumatology
- Joint, bone marrow or body cavity aspiration
- Manipulation of finger/shoulder dislocations
- Manipulation of arm-leg fractures/setting splints
- Migraine (acute ER treatment)
- Myocardial infarction/ischemic heart pain
- Nail trepanning
- Pain dressings and wound packs
- Posturing patients with severe pain on movement-e.g. spinal secondaries
- Radiation therapy-during transport to/from/during
- Removal of surgical drain
- Soft tissue injuries
- Staple application and removal
- Suture application and removal
- Urinary catherization

Has been safely used with patients having angina, ischemic heart pain, hypertension, rheumatic fever, heart murmur, congenital heart conditions, heart valve-pacemaker-bypass-transplant surgery, anemia, sickle cell, hemophilia, diabetes, thyroid gland dysfunction, hepatitis, ulcers, stroke, Parkinson's and seizure disorders; and in particular has been used/recognized for safe use with pediatrics

PATIENT MANAGEMENT ADVANTAGES OF SHORT TERM ANALGESIC USE OF 50% NITROUS OXIDE WITH DEMAND VALVE SELF ADMINISTRATION

N20 can manage both pain and anxiety

Very rapid onset of analgesia

Very rapid elimination and termination of effect

No known adverse reactions

Side effects are minimal in nature, and are rapidly self reversing/manageable

No allergic reaction to Nitrous Oxide ever reported

No drug incompatibilities; but its effect is incremental when used with other sedatives/opioids

No significant known physiological effects from short term use

- Remains unchanged in blood
- Blood flow to major organs is not effected; circulation is not depressed
- Cough and gag reflexes remain intact; no depression of respiration
- Doses in ambulatory short term use do not significantly effect blood pressure

Patient self administration system makes patient their own additional safety control; if N20 effect to great, patient cannot generate sufficient inhalation pressure (pull) on demand valve or press activation button anymore (system dependent), and mask/mouthpiece falls away from mouth

Premix in single cylinder produced in a pharma plant is QC'd based on procedures audited by regulatory authorities

Long history of safe use during birthing, with pediatrics for analgesia (dentistry), and with patients having a wide range and depth of medical conditions warranting emergency medical service transport

ACUTE ANALGESIC USE OF 50% N20: WHY IDEAL FOR TARGET ICD PATIENT USE IN UNSUPERVISED SITUATIONS

Depending primarily on N20 concentration used and level of pain/anxiety, if rapid deep breaths are taken

- Analgesia is initially produced in 20-40 seconds
- Peak clinical effects are seen in 2-3 minutes

With normal/slow rate and depth of breathing, achieving this same effect takes longer

After stopping administration the analgesia effect quickly subsides- the patient:

- After 90 seconds experiences a subsidence of effects
- After 3-5 minutes experiences weak or no perceptible drug effects
- After 20 minutes is at baseline of "0" re: any subtle physio or psych effects
- After 30 minutes can safely drive a car (extra 10 minutes provides further margin of safety)

The rate of elimination can be increased post administration by rapid deep breathing and/or 100% oxygen

PSYCHOLOGICAL PREPARATION OF PATIENT AFFECTS EFFECT

The effect of N20 is either enhanced or reduced based on the psychological preparation of the patient by their medical professional regarding what to expect

- If told there will be a positive effect on pain relief and anxiousness, positive results are enhanced
- If told there will be no to minimal effect, the effect of N20 is reduced

FEATURE/BENEFIT: EFFECTIVE PAIN RELIEF AND RAPIDLY REVERSING-MINIMAL SIDE EFFECTS OF 50% N2O WHEN USED FOR SHORT PERIODS OF TIME: EXAMPLES FROM THE LITERATURE

EXPERIENCE WITH SELF ADMINISTERED 50% N20 IN EMS TRANSPORT *

		EMS Administrations n = 1201		
Degree of Pain		Complete	Partial	None
Mild		36.1%	51.4%	12.5%
Moderate		28.8%	62.8%	8.4%
Severe		29.2%	61.6%	9.3%
Very Severe		25.6%	57.3%	17.1%
Partial to complete relief	90.4%			

* Includes fractures, wounds, chest pain, burns, etc.

N20 Conc.	Clinical Usage	Success in Self Administered Pain Control *
50%	Acute M I Pain	80% of patients had complete or partial relief
50%	EMS Transport Various Pain	Up to 93% of patients had complete or partial relief

ACUTE SHORT TERM USE OF 50% N20 AND CARDIAC RELATED APPLICATIONS*

The interaction of several cardiovascular functions such as contractility, output, stroke volume, heart rate and arrhythmias with N20 have been researched.

According to the dominant body of literature, short term acute use of 50% N20/50% O2 does not generate any significant physiological effects within the cardiovascular system

The minimally lowered cardiac output, HR and BP effects reported to be caused by the N20 in a mixture of 50% N20 and 50% O2 during ~10 minutes administration have been ascribed to the O2 in such a mixture rather then the N20, as they compare to the effects generated by high levels of O2 alone

"Physiological changes from 40% Nitrous Oxide in 60% 0xygen continuously inhaled for 10 minutes parallel those of 100% O2 inhaled for the same length of time"**

* Examples of sources:
1. Everett G et al. Simultaneous Evaluation of Cardiorespiratory and Analgesic Effects of Nitrous Oxide-Oxygen Inhalation Analgesia. J Am Dent Asoc. 1971: 83: 129-133
2. Thornton JA et al. Cardiovascular Effects of 50% Nitrous Oxide and 50% Oxygen Mixture. Anaesthesia, 1973: 28: 484-489
3. Kawamura R. et al. Cardiovascular Responses to Nitrous Oxide Exposure for Two Hours in Man. Anesth Analg 1980: 59: 93-99
4. Kerr K. et al. Nitrous Oxide Analgesia in Myocardial Infarction. Lancet 1972: 1: 63-66
5. Mitchell MA Nitrous Oxide Does Not Induce Myocardial Ischemia in Patients With Ischemic Heart Disease and Poor Ventricular Function. Anesthesiology, 1989, 71: 526-534
6. Kerr F et al. Nitrous-Oxide in Myocardial Infarction. Lancet, 1972, Jan, 63-65

** Everett GB, Allen GD, Simultaneous Evaluation of Cardiorespiratory and Analgesic Effects of Nitrous Oxide-Oxygen Inhalation Analgesia. JADA, vol 83, July 1971, 129-133

TYPICAL SHORT TERM ADMINISTRATION SIDE EFFECTS

INCIDENCE AND TYPES OF SIDE EFFECTS WITH SHORT TERM ~/<50% N20 FOR ANALGESIA

PATIENTS	Patients n = 1,060	
	#	% of Total
No side effects	981	92.5%
Nausea	41	3.8%
Emesis	14	1.3%
Dysphoria	7	0.6%
Mask claustrophobia	2	0.18%
Urine incontinence	2	0.18%
Increased apprehension	2	0.18%
Hallucinations	3	0.28%
Headache	3	0.28%
Dizziness	5	0.47%

One example ref. of what is typical in literature for short term use

No adverse reactions ever reported for N20; none in study reported in this paper

Administration time greater than AF ICD application

CONCEPT-VERY SHORT TERM ADMINISTRATION

TYPICAL ANALGESIA USING 50% N2O IS BASED ON ADMINISTRATION TIMES OF 10 MINUTES OR (MUCH) MORE TIME

FOR THE AF ICD APPLICATION, WE ONLY NEED TO BRING THE PATIENT TO THE INITIAL PEAK OF ANALGESIA WITH 2-3 MINUTES OF INHALATION

Dose = concentration plus administration time (time related to respiration rate and depth). The required concentration will likely be standardized; the time of inhalation will be dependent on the patients abilities to take deep breaths, and will be pre-evaluated/determined as to optimum dose with their physician.

DELIVERY SYSTEM CONCEPT FOR N20 GAS MIXTURE

FEATURES AND BENEFITS OF EXISTING PROTOTYPE

Usable with one hand

Compact enough for purse or attaché case

Lightweight (entire assembly with cartridge weighs less than 11 oz (cartridge size dependent)

Easy to use (minimal steps)

Failsafe

- Demand valve activated by patient
- Fixed N20 concentration and mixture unchangeable by patient

Gas container is fully disposable

Security re: abuse/mis-use of gas

- ICD activated chip in delivery device controls use
- Special cartridge/delivery device connection
- Physician can correlate # of shocks to cartridges shipped

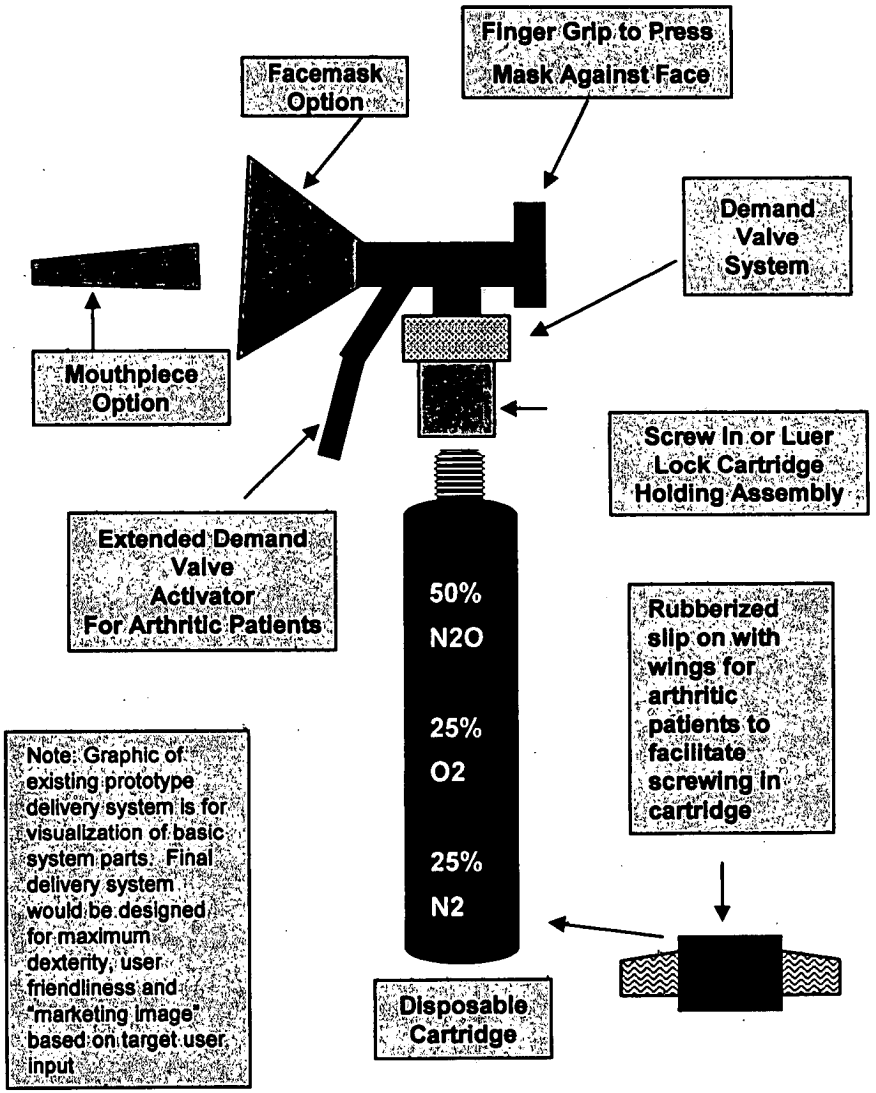
Can be shipped by First Class mail anywhere in the U.S.

Ideal for shipment to Medtronic patients at home

Permits E-Com re-ordering by physicians, or by their patients with physician approval/physician approved pre-set limits on # of cartridges

WHY 25% O2 AND 25% N2, vs. 50% O2

Reduce effect of 50% O2 on Heart Rate, Blood Pressure and Cardiac Output



Note: Graphic of existing prototype delivery system is for visualization of basic system parts. Final delivery system would be designed for maximum dexterity, user friendliness and "marketing image" based on target user input

PROCEDURE CONCEPT ONE: SHORT TERM CONSCIOUS ANALGESIA

PATIENT IS NOTIFIED BY ICD THAT THEY ARE IN AF

A CHIP IN THE DELIVERY DEVICE, ACTIVATED BY THE ICD, FREES THE DELIVERY DEVICE FOR N20 DELIVERY

THE PATIENT WOULD THEN INHALE FROM THE ADMINISTRATION DEVICE IN STEADY DEEP BREATHS USING THE DEMAND VALVE LEVER

THE PRE-DETERMINED FIXED DOSE OF N20 WOULD ALLOW THE PATIENT TO REMAIN CONSCIOUS AND SELF ACTIVATE THEIR SHOCK AT THE PEAK OF ANALGESIA

THE EFFECT OF THE N20 WOULD DISSIPATE OVER THE NEXT FEW MINUTES, BUT THEIR WOULD BE RESIDUAL EFFECT/BENEFIT IMMEDIATELY AFTER THE SHOCK

Dose = concentration plus administration time (time related to respiration rate and depth). The required concentration will likely be standardized; the time of inhalation will be dependent on the patients abilities to take deep breaths, and will be pre-evaluated/determined as to optimum dose with their physician.

PROCEDURE CONCEPT TWO: MOMENTARY SEMI CONSCIOUS/UNCONSCIOUS

PATIENT IS NOTIFIED BY ICD THAT THEY ARE IN AF

A CHIP IN THE DELIVERY DEVICE, ACTIVATED BY THE ICD, FREES THE DELIVERY DEVICE FOR N20 DELIVERY

PATIENT NOTIFIES EP BY REMOTE TELECOM OR TELEPHONE THAT THEY NEED TO BE DEFIBRILLATED, THE PATIENT LIES DOWN SOMEWHERE, AND REMOTE MONITORING OF PATIENT BEGINS

THE PATIENT THEN INHALES FROM THE ADMINISTRATION DEVICE IN STEADY DEEP BREATHS USING THE DEMAND VALVE LEVER

THE PATIENT WOULD REACH THEIR PEAK DOSE, BECOME SEMI-CONSCIOUS OR UNCONSCIOUS, THE DELIVERY SYSTEM WOULD FALL AWAY FROM THEIR MOUTH*

THE MONITORING EP OR MD WOULD THEN ACTIVATE THE ICD SHOCK BY REMOTE TELECOM (BASED ON PATIENT INHALATION TIME, 20 SECONDS OF DEMAND VALVE LEVER NOT BEING PRESSED, "0" GAS PRESSURE SENSOR, OR PHYSIO TELEMETRY)

THE SHOCK WOULD OCCUR DURING THE MINUTE OR TWO THE PATIENT IS SEMI-CONSCIOUS OR UNCONSCIOUS

PATIENT REGAINS FULL CONSCIOUSNESS, EFFECT OF N20 DISSIPATES OVER MINUTES